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Omics-Based Biomarker Discovery for Barrett's Esophagus: All Bark and No Bite?

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In the last 3 decades, the incidence of Esophageal Adenocarcinoma (EAC) has increased at a faster rate than any other cancer in the US and Europe [1-4]. Barrett's esophagus (BE), a condition in which the squamous epithelium of the distal esophagus is replaced by columnar epithelium with intestinal metaplasia, is a well-established risk factor for EAC. BE increases the risk of EAC by more than 40-fold [5,6]. The etiology of BE is not well characterized. Environmental factors, such as diet and obesity are associated with both BE as well as EAC [7]. The majority of patients with BE have a benign course, whereas 0.5% of patients per year progress from benign to malignant disease [8]. Critically, unless EAC is diagnosed before the invasion of the submucosal layer, it is associated with an abysmal outcome with <15% surviving beyond 5 years despite advances in treatment [9]. This has led to intensive global efforts focused on identifying biomarkers for risk stratification with the aims of reducing mortality from this disease. Early detection would allow for less invasive and less costly interventions. Encouraged by successes seen in other tumor types, many groups have embarked on ambitious omics-based approaches to identify clinically relevant biomarkers. The goal is to be able to distinguish clearly between BE patients who have low and high EAC risk. However, to date, while several biomarkers have been shown to be useful disease indicators, thus far, none have progressed to the stage of clinical implementation. A comprehensive review of current molecular markers that have been implicated in BE is beyond the scope of this editorial but extensively reviewed recently [10-13].

A common adage in clinical medicine is that when there is an excessive list of potential therapeutic options, it usually implies that none are any good. The same adage can be applied to biomarker discovery as exemplified in the case of BE. There are multiple reasons for the lack of validated biomarkers in BE predictive of EAC progression. Some of it reflects the natural history and pathophysiology of BE which makes it particularly challenging. Complicating many research studies is the lack of consensus regarding the definition of BE and if intestinal metaplasia should be a requirement for the diagnosis of BE [14]. Endoscopic measurement of the circumferential (C) and maximum (M) extent of Barrett's metaplasia remains an area of controversy. The recently proposed system for categorizing BE (Prague C and M criteria) has shown good interobserver agreement amongst endoscopists but still show poor agreement for shorter segments of esophageal columnar lining involvement [15]. There is no clear survival benefit of prospective screening or surveillance for BE [14]. The low rate of progression to EAC in BE also makes it hard to validate any molecular biomarkers and this is clearly reflected in that biomarkers in BE rarely make it to phases 3 and 4 of biomarker development (namely that of prospective screening studies and cancer control studies to address whether screening with biomarkers reduces the population burden of cancer). There is also controversy as to the cell of origin of BE as well as to the role clonal diversity plays in BE pathogenesis [16-18]. BE as an entity, thus, demonstrates significant somatic genetic and epigenetic heterogeneity, which results in many individual mutations and epigenetic marks being identified but no single marker or even set of markers has yet emerged. It is perhaps naïve to expect a single biomarker to be able to reliably predict for disease progression in such a complex disease as BE. This will likely require biomarker panels, but the questions remain: which molecular markers are truly informative; what should be included on panels; and how do we integrate such panels in clinical practice. This daunting task will require extensive multi-centre collaboration before any sensible conclusions can be reached.

The evolutionary theory of BE to EAC suggests that inherited changes in the constitutive (germline) genome and clonal somatic genomic instability in Barrett's epithelium leads to EAC. Indeed, the slow progress in finding the biomarker for EAC progression may stem from the great majority of investigation focused intently on the somatic genome and epigenome. Because somatic evolution is a stochastic process, the resulting molecular phenotype is inevitably unstable, making it difficult for reliable biomarker discovery. An approach to better understand the constitutive genome may instead be more fruitful. Indeed, at the level of the individual, there is substantial evidence for an inherited component to BE and EAC. These are based on case reports, twin studies, familial clusters and clinical series [19-24]. In one referral series, clinical epidemiologic analyses found that 7% of individuals with either BE/EAC have at least one affected blood relative [21]. Others have also shown that reflux disease in twins suggest a heritability of 30-40%, and that twins concordantly develop BE, suggesting a role for genetic susceptibility in both these conditions [25,26]. Furthermore, duplex and multiplex kindreds have a younger onset of disease compared with non-familial cases [27]. Practice guidelines have thus recommended that physicians treating BE or EAC take a detailed family history [22]. Indeed, we believe that germline genomic studies of affected patients and their family members, as well as studies focused on the germline genetics of apparently sporadic BE/EAC would accelerate the discovery of inherited genetic alterations that predispose to BE, EAC or both. Once identified, only those individuals with the germline alteration can be placed on screening and surveillance programs. Those individuals without the germline alteration need not undergo such intense surveillance. Such an approach would greatly hasten our understanding of the clinical utility of preventive screening and surveillance strategies as well as value-based healthcare delivery. Through integrative genomic analysis, our group has recently demonstrated the presence of germline mutations in *MSR1*, *ASCC1* and *CTHRC1* in 11% of patients with familial BE/EAC and are plausible

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candidate susceptibility genes for the 2 conditions [24]. These have provided insights into the underlying physiology of BE, encoding for proteins involved in apoptosis, innate immunity, polarity and mobility that affect inflammatory and TGF/WNT signaling pathways, both of which are implicated in BE pathogenesis [28]. At a population level, using a genome-wide association study (GWAS) approach, others have identified two novel determinants achieving confirmed genome-wide significance, one in the human leukocyte antigen (HLA) region and another on 16q24 (rs9936833), for which the closest protein-coding gene is *FOXF1*, which is implicated in esophageal development and structure [29]. While inference of the underlying genes must be taken with caution until further validation, both these studies demonstrate direct evidence that BE/EAC etiology has a genetic component.

There is substantial evidence that evolution of EAC is associated with potentially modifiable host and environmental risk (e.g. obesity) and protective factors (e.g., aspirin) in the population. To better understand the biology of BE and the progression to EAC, we will need large-scale efforts to better understand how genetic susceptibility interacts with environmental factors. *Helicobacter pylori* infection has been reported to be associated with an increased risk of gastric adenocarcinoma and decreased risk of EAC [30]. In fact, 10% of the genome in and on our bodies is non-human, the so-called metagenome. Human beings harbor trillions of microorganisms that live in a symbiotic relationship with the host in body surfaces and cavities connected with the external environment [31-34]. Escalating evidence from these metagenomic studies show that disruption of the homeostasis between the microbiota and the host can have a more important role than host genetics in the development of diseases such as inflammatory bowel disease, metabolic syndrome and is involved in the initiation and progression of cancer. Using metagenomic profiling, others and we have demonstrated that specific microbial subpopulations can be seen in cancer patients compared to controls. Tantalizingly in head and neck squamous cell carcinomas (HNSCC) compared to paired normal mucosae, *MDR1* methylation was shown to be associated with specific microbial subpopulations in HNSCC, suggesting the hypothesis that such microbiomic populations may trigger inflammation with consequent promoter hypermethylation of *MDR1* and potentially other tumor suppressor genes [35]. Recent research also suggests that the microbiome of the distal esophagus is different in health and disease [36].

A truly integrative approach taking into account both host as well as environmental genomics may allow us to make true inroads into our current understanding of BE/EAC. If indeed, we do find metagenomic changes which are predictors for BE and/or EAC, this would provide long awaited mechanistic insights into understanding metaplasia and the development of cancer in BE. More critically, it can pave the way for novel probiotic/ antibiotic approaches for chemoprevention for those at increased risk. Only then, would we have truly "sunk our teeth" into the complex and deadly conundrum of which subset of BE would transform to EAC.

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